II. Preliminary Remarks/Interview Summary

Applicants thank the Examiner for an interview on February 22, 2008, during which the following was discussed: the pending claims, amendments to the claims and the art cited against the claims. No agreement was reached.

With this response, Applicants cancel claim 44 and replace it with new claim 54 which finds support in canceled claim 44 and throughout the specification as filed.

III. Patentability Arguments

A. The Rejection Under 35 U.S.C. § 112, Second Paragraph, Should Be Withdrawn.

The Examiner rejected claim 44 under 35 U.S.C. § 112, second paragraph, alleging that the claim is indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The Applicants respectfully disagree with the Examiner; however, in the interest of expediting prosecution with this response, Applicants have canceled claim 44 and replaced it with claim 54, therefore, the following remarks are made with respect to new claim 54.

At page 3 of the Office Action, the Examiner alleges that it is unclear whether "bacteriophage particles" are structural parts of the "recombinant host cells." Claim 54 recites "recombinant host cells each of which harbors a phagemid." Bacteriophage particles are produced in and secreted from the host cells when infected by helper phage.

At page 3 of the Examiner further alleges that the term "phagemid genome" is not clear as was recited by claim 44. New claim 54 explicitly recites

> "a phagemid comprising a nucleic acid fragment encoding one member of a specific binding pair fused to a nucleic acid encoding a gene III coat protein surface component of a filamentous bacteriophage and further comprising an origin of replication of a filamentous bacteriophage, "*...the gene III coat protein surface component encoding nucleic acid and the origin of replication being the only nucleic acid in the phagemid derived from filamentous bacteriophage....*" (Emphasis added.)

Thus, the recited phagemid contains only two regions derived from filamentous bacteriophage genome: a gene III coat protein encoding nucleic acid and an origin of replication.

In conclusion, the Applicants submit that claim 54 meets all of the requirements of 35 U.S.C. § 112, second paragraph and, therefore, the Examiner may properly withdraw the rejection under 35 U.S.C. §112, second paragraph; and withdrawal is respectfully requested.

B. The Rejections Under 35 U.S.C. §§ 102(b) and (e) Should Be Withdrawn.

The Examiner rejected claims 44 and 45 as allegedly being anticipated by Smith, *et al.*, *Science*, 228:1315-1317 (June 14, 1985); Parmley, et al, *Gene*, 73:315-318, (1988); and Ladner, *et al.*, U.S. Patent No. 5,223,409. The Applicants respectfully traverse the rejections and request reconsideration in view of the present amendments and remarks.

1. Smith et al.

The Examiner stated that *Smith* teaches throughout the publication phage displaying antigens which are screened for specific binding antibodies (abstract).

- teaches inserting a nucleic acid encoding for (sic) an antigen (such as a fragment of a endonuclease which antigen reads on the "one member of specific binding pair (claim 44) because the antigen binds to a specific antibody (i.e., the other member of the specific binding pair member);

- teaches using filamentous phage and fusing the antigen with the geneIII coat protein (p. 1315, cols. 1-2), which reads on the phage and the geneIII coat protein of claim 44;

- teaches host cells to grow phage particles (claims 1-5) which reads on the "recombinant host cells of claim 44;

- teaches using the genome of phage f1 (co. 1, last paragraph) which reads on the phagemid genome; and

- teaches mutating the insertion (col. 2) which reads on the limitation of claim 45.

Claim 44 is canceled with this response. Newly added claim 54 recites a limitation that each displayed member comprises "a functional specific binding domain," which *Smith et al.* fails to teach.

At page 30, lines 19-29, of the specification, the Applicants define "functional" as

"In relation to a sbp member displayed on the surface of a rgdp, means that the sbp member is presented in a folded form in which its specific binding domain for its complementary sbp member is the same or closely analogous to its native configuration, whereby it exhibits similar specificity with respect to the complementary sbp member. In this respect, it differs from the peptides of Smith et al, supra, which do not have a definite folded configuration and can assume a variety of configurations determined by the complementary members with which they may be contacted." (Emphasis added.)

At page 6 of the Office Action, the Examiner quotes *Lehninger et al.*, "Biochemistry" which defines the term "domain" as "*a distinct structural unit* of a polypeptide" and further explains that "domains" may hold a separate function. Applicants bring to the Examiner's attention that the meaning of the term "distinct structural unit" is well understood by a person of ordinary skill in the art to mean a unit of amino acids which form a separate tertiary structure. For example, a zinc-finger domain is a distinct structural unit because it forms a finger-like structure when coupled with zinc. Therefore, the sequence of amino acids that forms a zinc-finger structure is a domain. But if only half of the sequence that forms a zinc-finger structure is expressed in a phagemid, the expressed polypeptide is not a "functional specific binding domain" because the polypeptide cannot form a distinct structural unit, the zinc-finger structure which allows binding to zinc. Despite not being a domain, the so expressed polypeptide can still be used to generate polyclonal antibodies against it. The polypeptide can still bind the antibody that is generated against the peptide because it is possible to generate antibodies against polypeptides that are denatured and do not form any tertiary structure at all, but it is not the same or closely analogous to its native configuration.

Claim 54 recites display only of functional domains or in the words of *Lehninger* only of distinct structural units of a protein, as explained in the specification. Under this definition, the claim would include the display of a zinc-finger domain, but not the display of a polypeptide which contains only half of the zinc-finger domain sequence.

As discussed in detail in the previous response, *Smith* does not disclose the display of a functional domain which must be properly folded in order to be functional.

Instead, Smith demonstrated the display of a 171bp Sau3A fragment of *E. coli* EcoRI endonuclease. Examination of the DNA sequence of EcoRI endonuclease (A.K. Newman *et al., J. Biol. Chem.* 2562131-2139 (1981)) indicates that this would correspond to amino acids 76-133 of the protein.

The X-ray crystal structure (Y.C. Kim *et al., Science* 249:1307-1309 (1990)) indicates that this region would contain just two strands of a three strand anti-parallel beta-sheet which forms part of a larger five strand beta sheet structure. Thus an incomplete and non-functional fragment would have been displayed by *Smith* which would not have contained the amino acid sequences which are involved in binding of the protein to DNA (residues 103-241). The fragment of EcoRI endonuclease displayed on phage is recognized in the *Smith* paper by a polyclonal antiserum which would be expected to contain antibodies which would recognize linear epitopes which did not need to be folded to achieve their native structure. Thus, *Smith* does not display a properly folded functional binding domain and cannot properly anticipate the present invention.

Further, the Examiner asserts that *Smith* uses the genome of fl which reads on the phagemid genome. However, the *Smith* phage which comprises a full phage genome is not a phagemid. Further, the *Smith* display of a polypeptide does not require the use of a helper phage as recited by the pending claims. The pending claims provide that "upon infection of said recombinant host cells with a helper phage, the phagemids are each packaged into filamentous bacteriophage particles displaying on their surface the functional specific binding pair member." Further, the phagemids of the present claims contain only an origin of replication and a nucleic acid encoding a gene III coat protein and not the full phage genome. Therefore, *Smith* simply does not teach or suggest the use of phagemids as presently claimed.

In conclusion, because *Smith* does not disclose at least several limitations of the instant claims, *Smith* cannot anticipate the claims and, therefore, the rejection over *Smith* under 35 U.S.C. §102(b) can be properly withdrawn; and withdrawal is respectfully requested.

2. *Parmley et al.*

The Examiner also alleges that *Parmley* anticipates the subject matter of claims 44 and 45 because it teaches:

- inserting a nucleic acid encoding for an antigen (such as fragments of β-gal protein which the (sic) antigen reads on one member of a specific binding pair;

- teaches using filamentous phage and fusing the antigen with the Gene III coat protein;

- teaches using recombinant host cells of claim 44;

- teaches using the genome of phage which reads on the phagemid genome; and

- teaches mutating the insertions which reads on the limitation of claim 5.

As is the case with *Smith et al.*, *Parmely, et al.*, fails to teach the display of a functional specific binding domain. *Parmley* discusses display of a 335bp fragment of beta-galactosidase corresponding to nucleotides 861-1195 in the gene sequence. This fragment of a gene encodes 112 amino acids of a much larger 380 amino acid domain. Thus, only a fragment and not a functional domain is displayed, and that which is displayed has none of the functions of beta-galactosidase or any of its domains. Thus, there is no evidence that *Parmley* ever displayed a properly folded functional specific binding domain as is required for the present invention.

Furthermore, newly added claim 54 recites a phagemid which comprises only two nucleic acid sequences derived from a phage and which must be rescued with a helper phage for the proper display of a binding member on the surface of a filamentous bacteriophage. *Parmley* does not disclose the use of a helper page and further, the *Parmley* does not utilize a phagemid as is required by the present claim.

In conclusion, because *Parmley* does not disclose at least several limitations of the instant claims, *Parmley* cannot anticipate the claims. Therefore, the rejection over *Parmley* under 35 U.S.C. §102(b) can be properly withdrawn and withdrawal is respectfully requested.

3. *Ladner et al.*

Claims 44 and 45 were rejected under 35 U.S.C. § 102(e) as allegedly being anticipated by *Ladner*. Claim 44 is canceled with this response and newly added claim

54 recites a limitation to '[r]ecombinant cells each of which harbor a phagemid which comprises the gene III coat protein surface component encoding nucleic acid and the origin of replication being the only nucleic acid in the phagemid derived from filamentous bacteriophage,..." and which is packaged into filamentous bacteriophage upon infection of recombinant host cells with a helper phage.

Ladner discloses a method in which phagemids, unlike those of the present invention (in which the only phage derived sequences are an origin of replication and a gene III encoding nucleic acid), comprise the full bacteriophage genome and further states that those which do not contain the full genome are not suitable for the *Ladner* methods.

The passages (column 76, lines 55-67) of *Ladner* specifically state that phagemids are not suitable for the purposes of the present invention:

> "Phage prepared from these cells would be designated XY24. Phagemids such as Bluescript K/S (sold by Stratagene) are not preferred for our purposes because Bluescript does not contain the full genome of M13 and must be rescued by coinfection with competent wild-type M13. **Such coinfections** could lead to genetic recombination yielding heterogeneous phage **unsuitable for the purposes of the present invention** (emphasis added)

At page 13 of the Office Action, the Examiner states that a non-preferred embodiment of the prior art's teaching constitutes prior art. The Examiner then states that *Ladner* discloses the phagemid recited by the pending claims as a non-preferred embodiment because it states phagemids such as Bluescript are not preferred for our purposes. However, this quoted sentence from *Ladner* should be considered in the context of the rest of the *Ladner* disclosure, as quoted above. As can be seen from the quoted passage, *Ladner* specifically states that the usage of a helper phage is unsuitable for the purposes of the present invention. While *Ladner* specifically states that a helper phage is unsuitable for its invention and consequently only those phage that do not need to be rescued with a helper phage can be used, the present claims are limited only to a phagemid with must be rescued by the helper phage and in which the only bacteriophage derived sequences are a gene III protein encoding nucleic acid and an origin of replication.

Because *Ladner* specifically excluded the use of a phagemid as recited by the pending claims and does not describe phagemids as presently claimed, *Ladner* cannot anticipate the pending claims. Therefore, the Examiner may properly withdraw the rejection of the pending claims under 35 U.S.C §102(e) over *Ladner;* and withdrawal is respectfully requested.

C. The Rejections Under 35 U.S.C. § 103(a) over *Parmley* and *Ladner* (WO88/06630) Should be Withdrawn.

The Examiner rejected claims 44-53 under 35 U.S.C. § 103(a) as allegedly being unpatentable over *Parmley* in view of Ladner WO88/06630 (*Ladner* WO). Claim 44 is canceled with this response.

The Examiner characterizes using phage particles to display proteins of various sizes as discussed above. However, as discussed above, *Parmley* does not teach, *inter alia*, the display of "functional specific binding domains" which by definition are properly folded functional polypeptides (see sections III B1, *et seq.*).

The Examiner has characterized *Ladner* WO as teaching the use of lambda phage to display antibody fragments such as single chain antibodies, teaching generating a large repertoire of genes encoding for single chain antibodies and displaying the antibodies on the surface of phage.

The Examiner then concludes by stating that it would have been *prima facie* obvious for one of ordinary skill in the art to generate recombinant cells comprising phage display particles displaying binding domains of antibodies or immunoglobulin or single chain antibodies.

As discussed above in detail in Section III B, *et seq.*, *Parmley et al.*, *inter alia*, does not disclose a display of a "functional specific binding domain on a filamentous bacteriophage...."

Ladner WO does not disclose the rescue of a phagemid by a helper phage which phagemid is packaged into a filamentous bacteriophage. *Ladner WO* discloses only display on a lambda phage which is physiologically distinct from filamentous bacteriophage. Lambda phage are lytic for their host cells, that is, when lambda replicates and phage particles are released from the host cells, the host cell wall is

destroyed and the cell is lysed. Filamentous phage, however, are not lytic for their host cells and are assembled at and extruded from the surface of the host cell leaving the host cell intact. This has important implications with respect to the display of functional domains in that in contrast to the physiological conditions at the cell surface where filamentous bacteriophage are assembled, lambda is assembled in the cytoplasm of the host cell which is a reducing environment which can influence the ability of certain polypeptide to fold properly into functional domains. Because protein folding is problematic in the reducing environment and *Ladner* WO discloses only display in lambda phage in which a binding member folding is to occur in the reducing environment, *Ladner* WO does not disclose the display of a functional domain.

In summary, the *Parmley/Ladner* WO combination does not teach or suggest at least several limitations of the instant claims and therefore, the *prima facie* case for obviousness has not been established. The Examiner may properly withdraw the rejection of the pending claims under 35 U.S.C. §103(a) over the *Parmley/Ladner* WO combination; and withdrawal is respectfully requested.

IV. Conclusion

In view of the above amendments and remarks, Applicants respectfully submit that the instant application is in good and proper order for allowance and early notification to this effect is solicited. If, in the opinion of the Examiner, a telephone conference would expedite prosecution of the instant application, the Examiner is encouraged to call the undersigned at the number listed below.

Respectfully submitted,

HOWREY LLP

By: /David W. Clough, Ph.D./Reg. No. 36,107
David W. Clough, *Ph.D.*
Registration No.: 36,107
Customer No.: 22930
Telephone No.: (312) 595-1408

Dated: March 14, 2008

HOWREY LLP
ATTN: Docketing Department
2941 Fairview Park Drive, Suite 200
Falls Church, VA 22042-9922
Telephone No.: (703) 663-3600
Facsimile No.: (212) 383-7195